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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/730,267	12/09/2003	Stephan Brunner	1866.0450000/PEG/CMB	3322

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EXAMINER

BORIN, MICHAEL L

ART UNIT	PAPER NUMBER
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1631

DATE MAILED: 06/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/730,267

Applicant(s)

BRUNNER ET AL.

Examiner

Michael Borin

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-18 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-16 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date ____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: ____.

DETAILED ACTION

Status of Claims

Claims pending are 1-16.

Claim Rejections - 35 USC 112, second paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection is applied for the following reasons:

- A. Claim 1, step (a): the term "sampling" is vague and indefinite. The specification, although providing particular examples, does not provide a standard for ascertaining the requisite method step, and one of ordinary skills in the art would not be reasonably appraised of the scope of the invention.
- B. Claim 1, step (b): It is not clear how an value for fragment-residue pairs can be deduced from step a) if step a) is directed to sampling of interaction of entire polypeptide with a fragment, whereas the subsequent step b) is expected to assign affinity values for each residue of polypeptide.
- C. Claim 7: The claim is indefinite, because it uses abbreviations which are not explicitly disclosed in the specification.

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D. Claim 15: the term "fragment types" is vague and indefinite. It is not clear what "types" of fragments are being averaged, and one of ordinary skills in the art would not be reasonably appraised of the scope of the invention.

Claim Rejections - 35 U.S.C. 101 (Non-statutory subject matter)

Claims 1-16 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The method of claims 1-10, 23, and 27-33 is merely a mathematical manipulation of data. The apparent series of mathematical steps for the data manipulation is equivalent to a mental process. Applicant is reminded that mental processes are not statutory subject matter under 35 USC 101. In the event that the claimed method steps are implemented by a computer, the method steps are not statutory as any computer implemented method must produce a result which is concrete, tangible, and useful (MPEP 2106.IV.B). The claimed method is directed to a method for analyzing binding affinity between peptides and molecular fragments, but does not identify either the outcome of the method (rather than e.g., "assigning value step"), or particular polypeptides information of which is entered into computer. As claims recite only mathematical manipulation of data, and do not recite a concrete, tangible and useful result, the claims are not statutory.

Claim Rejections - 35 U.S.C. 101 (Lack of utility)

Claims 1-30 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

The claims are directed to a method for analyzing binding of a molecular fragment to polypeptide. The claims do not recite any steps of identifying ligands, any particular proteins to which a ligand is docked, or any other result of the method. An *in silico* method to screen libraries of compounds for a particular activity (e.g. inhibition/activation of a protein with known activity) would have a patentable utility. However, as set forth above, the instant claims do not recite any particular protein for which ligand binding/docking is evaluated. The claims do not recite any selection, screening, identification, etc. steps for any set of ligands docked to a protein. A method of identifying or designing a receptor for a ligand with a known function (utility) would also have utility under 35 USC 101. However, the claims do not recite any particular ligands, and do not recite any steps of identification or design of either a ligand or a receptor. "Analyzing" interaction of molecular fragments and polypeptide residues in terms of energy-related scoring is not a substantial utility as it would require further research. See, for example Abagyan et al (Curr Opin Chem Biol. 2001 Aug;5(4):375-82) reference which teaches:

It has been shown repeatedly that most scoring functions fail to show significant correlations with binding constants when confronted with novel ligand-receptor systems, even though they are generally tuned well to predict binding constants for a training set.

p. 378, section "Scoring".

Thus, any assigned values determined according by the claimed method would need further research to be utilized. More so, results value that are averaged from families of

(unrelated?) molecular fragments, as per claims 14-16, would require more subsequent research to identify their concrete, tangible, and useful result.

As set forth above, the instant claims do not recite what the "effect" itself is, or what it is intended to act upon. The claims do not recite dependent or independent variables. A claim which merely recites estimating the effects of an independent variable on a dependent variable, where the variables are not identified, would not have a utility as further research would be required to determine what the effect is. As set forth in MPEP 2107, a "use" to do further research is not a utility under 35 USC 101. As applicant has failed to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention, the claims lack utility. See MPEP 2107.01, and the analyses of utility in *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (1966) and *In re Ziegler*, 992 F.2d 1197, 26 USPQ2d 160U (Fed. Cir. 1993). The claims merely recite steps of data manipulation, on a dataset of unknown provenance, and do not produce a concrete, tangible, and useful result.

Claim Rejections - 35 USC 102 and 103.

The following is a quotation of the appropriate paragraphs of 35 U.S.C.102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section

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351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1,14 are rejected under 35 U.S.C. 102(e) as anticipated by Floriano et al (US 2002/0099506; 11/30/2001).

The instant claims are drawn to method for determining affinity between polypeptide amino acid residues and at least one molecular fragment comprising calculating interaction energy between polypeptide and a fragment, wherein the fragment is located in the vicinity of the polypeptide's residue and assigning affinity value which is a measure of the free energy of interaction between polypeptide and molecular fragment. Further, dependent claims 2-8 address determination of threshold

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distance between residue and fragments based on van der Waals distances and force field calculations. Furthermore, claims 9-12 address use of Boltzman energy equation for calculation of affinity value.

Floriano et al teach method of modeling ligand protein binding interactions. The method includes steps of using docking techniques and generating initial conformations for one or more ligands known to bind the protein; scoring an energy function for each of the best conformations; and identifying the probable binding site based on a spatial location of the conformations having the lowest energy scores. [0010]-[0012]. Thus, Example 1 describes steps of using DOCK 4.0 software to calculate energy of interaction of various conformations (and thus various molecular fragments) of ligand (phenylalanine) with polypeptide, scoring interactions of said various conformations and ranking interaction using energy scoring. Further, improved scoring is achieved by using a full atom forcefield, such as AMBER, CHARMM, DREIDING or MM3. See p. 6, Example 1, and p. 1, [0007].

It is the Examiners position that all the elements of Applicant's invention with respect to the specified claims are instantly disclosed by the teaching of the references cited above.

Claims 1,14 are rejected under 35 U.S.C. 102(e) as anticipated by Guarnieri et al (US 6735530; filing date 09/23/1998).

Guarnieri teaches method for identifying binding sites on a macromolecule (such as polypeptide) comprising identifying candidate sites for binding ligand molecules by simulated annealing of chemical potential calculations for at least one organic fragment (ORF), identifying locations at which the relevant ORF is strongly bound, and outputting results. See claims 1-9. The simulations are conducted at separate values of parameter B, wherein B is related to excess chemical potential $\mu'/kT+1$. The method can be conducted with plurality of ORFs and is repeated for plurality of sampling sites of macromolecule (i.e., polypeptide). The results are outputted as a list of molecular fragments and sampling sites.

It is the Examiners position that all the elements of Applicant's invention with respect to the specified claims are instantly disclosed by the teaching of the references cited above.

Claims 1,14 are rejected under 35 U.S.C. 102(b) as anticipated by Apostolakis et al (Journal of Computational Chemistry, Vol. 19, No. 1, 21-37,1998).

Apostolakis teaches method for docking ligands in a flexible binding site. The algorithm seeds the ligand near the putative binding site, allowing structures to occur in which ligand atoms overlap with the protein. The ligand molecule is and its center of mass is moved to the center of a 10.0 A radius sphere that contained the binding site of the protein. About 1000 seed structures (i.e. molecular fragments) is generated by rotating ligand and displacing by a randomly oriented vector of random length between 0 and 10 A. The proximity between ligand and protein atoms is evaluated based on

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Lennard-Jones potential. The minimized structures are evaluated according to an approximated free energy G , which includes total energy of the CHARMM force field. The electrostatic contribution to the solvation free energy G is obtained by numerical solution of the linearized Poisson-Boltzmann equation using iterative algorithm and atomic radii and partial charges obtained from CHARMM22 force field.

It is the Examiners position that all the elements of Applicant's invention with respect to the specified claims are instantly disclosed by the teaching of the references cited above.

Claims 2-13 are rejected under 35 U.S.C. 103(a) as obvious over Apostolakis et al, or Floriano et al, or Guarnieri et al, in view of Fahmy et al (J American Chemical Society (2002), 124(7), 1241-1250)

The references do not specifically teach establishing predetermined threshold distance defined by van der Waals radii. However, the referenced methods place ligand fragments in the vicinity of polypeptide. See, for example Apostolakis et al, p. 23, section "Seeding". Further, it is well known that successful docking requires interacting molecules to be within close proximity which, however, has a lower limit defined by van der Waals interaction. See, for example Fahmy et al (p. 1242, right column). Therefore, it would be obvious that, if desired, a definition of allowed threshold distance in calculations of interactions of polypeptide and molecular fragment can be included in method of analyzing.

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Further, with respect to claims 4-6, it would be obvious to determine all operable distances because docking distance is an art-recognized result-effective variable which is routinely determined and optimized in the process of computer modeling of docking. It would have been obvious to one of ordinary skill in the art at the time applicants' invention was made to determine all appropriate distances as it is required for successful docking of a ligand.

Further, with respect to claim 8, it would be obvious to use any available functionally equivalent software for calculating force field. See Floriano et al., for example.

Further, with respect to claims 10,11, it would be obvious to determine density of fragments per residues because it is an art-recognized result-effective variable which is routinely determined and optimized in the process of computer modeling of docking. It would have been obvious to one of ordinary skill in the art at the time applicants' invention was made to determine all appropriate densities of fragments as it is required for successful docking of a ligand.

Double Patenting

Claims 1-16 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-18 of copending Application No. 10/920234.

This is a provisional obviousness-type double patenting rejection.

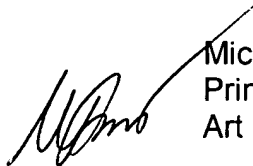
Conclusion.

No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D., can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Michael Borin, Ph.D.
Primary Examiner
Art Unit 1631

mlb